UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/665,493 | 09/20/2000 | William C. Manning JR. | PP01588.005 (20263-40) | 1563 |

27476 7590 03/07/2003

Chiron Corporation
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097

| EXAMINER |
|---|
| TON, THAIAN N |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | |

DATE MAILED: 03/07/2003

20

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/665,493 | MANNING ET AL. | |
| | Examiner | Art Unit | |
| | Thaian N. Ton | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *06 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *1-16, 23-25, 30-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-22 and 26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 September 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☒ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6, 13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

Claims 1-44 are currently pending.

Claims 1-16, 23-25 and 30-44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 14.

Claims 17-22 and 26-29 are under current examination.

### *Election/Restrictions*

Applicant's election with traverse of Group II, Claims 17-22 and 26-29 and the species of soluble Flt-1 in Paper No. 14 is acknowledged. Applicant's election of Group II, Claims 17-22 and 26-29 and the species of soluble Flt-1 in Paper No. 14 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-16 and 23-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 14.

### *Priority*

The priority should be updated to reflect that U.S. Patent No. 09/525,956 is now abandoned. See p. 1, line 5 of the specification.

*Specification*

The disclosure is objected to because of the following informalities:

p. 8, line 4 of the specification does not have a SEQ ID NO.

Appropriate correction is required.

*Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting neovascularization in the eye, comprising the intraocular co-administration of an AAV-vector which directs the expression of VEGF and an AAV-vector which directs the expression of soluble Flt-1, wherein the simultaneous administration of the vectors inhibits neovascularization in the eye, the specification does not reasonably provide enablement for methods of inhibiting neovascular disease of the eye comprising administering intraocularly a gene delivery vector which directs the expression of an anti-angiogenic factor, such that neovascular disease of the eye is inhibited. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claimed invention is directed to methods of inhibiting neovascular diseases of the eye comprising administering intraocularly a gene delivery vector which directs the expression of an anti-angiogenic factor, such that the neovascular disease of the eye is inhibited. In further embodiments, the neovascular disease of the eye is diabetic retinopathy, wet AMD and retinopathy of prematurity (claim 19), the anti-angiogenic factor is soluble Flt-1 (claims 18, 26) and the gene delivery vector is a retroviral vector selected from the group of HIV and FIV (claims 20, 27 and 28), or a recombinant adeno-associated viral vector (claims 21 and 29).

The specification teaches methods to treat, prevent or inhibit disease of the eye by intraocularly administering a gene delivery vector, such as those generated from retroviruses, adenoviruses or adeno-associated viruses, wherein the gene delivery vector directs the expression of one or more neurotrophic factors or anti-angiogenic factors (see page 5 of the instant specification). The specification further discusses general construction of various gene delivery vectors (see pp. 13-17), and methods of administering a gene delivery vector to the eye (see pp. 20-22). The specification teaches the construction of various rAAV vectors expressing neurotrophic factors FGF-2, FGF-5 and FGF-18 after infection of 293 cells (Examples 1-4). The specification teaches that albino Sprague-Dawley rats were

subretinally injected with 2-3 μl of AAV-CMV-Lac-Z vector and cryosections of the retina were stained for β-galactosidase presence (Example 5). The specification teaches that line 3 albino transgenic rats (P23H-3) on an albino Sprague-Dawley background were subretinally and intraocularly injected with a rAAV vector expressing FGF-2 and it was found that the injected rAAV vector produced a rescue effect on degenerating photoreceptor cells when compared to the control, uninjected eyes (see Example 6). The specification teaches that s334ter-4 albino transgenic rats, which have a mutation that is similar to rhodopsin mutations found in a subset of patients with retinitis pigmentosa, exhibit a phenotype of photoreceptor death and retinal degeneration which begins at postnatal day 10-15, were injected with either a vectors expressing FGF-5 or FGF-18 and either a control vector containing no neurotrophin, injection of PBS, or no injection. The eyes of the rats were removed and analyzed and it was found that injections of both the vectors containing FGF-5 and FGF-18 resulted in a rescue of photoreceptors when compared to controls (see Example 8 and Figure 33). The specification specifically teaches that soluble FLT-1 (sFlt-1) receptor was cloned into the pD10-CMV rAAV vector (Example 14).

The specification further teaches the generation of a rat model that exhibits subretinal neovascularization and choroidal neovascularization, which are hallmarks of diabetic retinopathy, retinopathy of prematurity and wet age-related macular degeneration, respectively. The specification teaches that subretinal

injections of 2 μl of AAV-VEGF were made 3-3 ½ months prior to sacrifice of the rats. After sacrificing, the rats were examined for the extent and duration of neovascularization induced by the rAAV vectors using fundus photography, fluorescein angiography, histology and immunochemistry [see Figures 35-37]. It was found that retinal blood vessels from these animals were larger than blood vessels of the control animals, and epoxy sections show new blood vessel growth [see Figure 36]. The specification further teaches the co-injection of either rAAV-sFlt-1 or rAAV-PEDF vectors with the rAAV-VEGF vector into the subretinal space of one eye. The contralateral eye received an injection of rAAV-VEGF and rAAV-GFP. Six weeks after the injection, both eyes were obtained and analyzed. The a- and b-wave amplitudes were measured by electroretinographic analysis [see Figure 38]. The specification teaches that there was significant functional rescue obtained in three out of four animals using the sFlt-1 vector [see Figure 39].

The claims are directed to methods of inhibition of neovascular disease. Although the specification provides an example wherein simultaneous co-injection of two vectors, one containing VEGF and one containing Flt-1, show functional rescue, the specification fails to provide teachings or guidance for the breadth of the claimed methods which encompass all stages of disease. In particular, the specification provides a scenario wherein one would expect the rat model to develop neovascular disease, and the injection of the Flt-1 vector inhibits the formation of this disease. However, the model never develops neovascular disease prior to Flt-1

vector administration. If the model never develops neovascular disease, then it is not seen as how the model is a representation of all forms of "inhibiting". The specification provides no teachings or guidance as to how to correlate the results presented in the specification with the inhibition of ongoing neovascular disease in a patient. For example, there are no teachings or guidance provided by the specification with regard to which individuals would be at risk for developing neovascular disease, such that the disease could be inhibited prior to the onset, or at what stage of neovascular disease onset the administration of Flt-1 would need to occur in order to prevent neovascular disease. The specific guidance is to inhibiting the onset of neovascular disease by inhibition of angiogenesis prior to the occurrence of angiogenesis. Note that inhibition is a form of treatment of neovascular disease. As such, the example provided by the specification, wherein co-injection of the two described vectors inhibits the formation of neovascular disease in the eye, does not provide a correlation with inhibition of neovascular disease in an individual who may potentially develop the disease, not in an individual who has experienced neovascularization. The specification provides no teachings or guidance to show that injection of the sFlt-1 vector to the rat model that already exhibits neovascularization in the eye would show a functional rescue. The specification teaches that inhibition is to result in the functional rescue of the eye. However, the model as taught by the specification cannot correlate with functional rescue of the eye, as no eye function is ever lost in the rat model. This

exemplified inhibition is not representative of treatment or inhibition in a patient who develops neovascularization in the eye *de novo*, prior to detection, and the administration of sFlt-1 post-neovascularization.

The claims are directed to gene therapy, however, it is noted that numerous factors complicate *in vivo* gene transfer and expression which result in therapeutic effects. Romano *et al.* (**Stem Cells**, 1999, 17 :191-202) review the state of the art of gene therapy, noting that although gene therapy has attracted much interest since the first clinical trials, "However, gene delivery systems still need to be optimized in order to achieve effective therapeutic interventions." (see *Abstract*). Romano *et al.* further state that, "Although much effort has been directed in the last decade toward improvement of protocols in human gene therapy, and in spite of many considerable achievements in basic research, the therapeutic applications of gene transfer technology remains mostly theoretical." (See p. 192, 1st column, 3rd paragraph). Romano *et al.* discuss the importance of tailoring a gene therapy vector and method for specific disorders and/or diseases (see p. 192, 2nd column, *Gene transfer models*) and review the characteristics and disadvantages of the currently available gene delivery systems (see Table 1, page 193). Romano *et al.* note that unpredictable factors such as the particular vector system used, as well as the *in vivo* expression of the vector have not been shown to be overcome by routine experimentation (see p. 194, 1st column). Romano *et al.* conclude that, "The standpoint of gene therapy basic research is still far from providing the tools for the

treatment of the previously mentioned illnesses. The most pressing issue that the field of gene therapy has to address is the development of efficient *in vivo* delivery systems." (See p. 198, *Conclusion*, last paragraph).

With particular regard to the claimed invention, Ali *et al.* (**Br J Opthalmol**, Vol. 81, September 1997, pages 987-801) state that gene therapy for certain diseases of the eye will be realized sooner than others, and in particular, "Gene therapy for inherited retinal degenerations, where there is requirement for long term gene expression with appropriate regulation, will present considerable difficulties." (See p. 2, 1st pagraph, lines 3-5). Ali *et al.* further evaluate different vectors used for ocular gene therapy, and in particular state that, with regard to retroviral vectors, "Retroviruses are ssRNA viruses which require cell division for transfection; recombinant retroviruses are therefore limited in their use for *in vivo* gene transfer as ocular tissues are either terminally differentiated or divide very slowly." See p. 3, 2nd paragraph. Furthermore, with regard to adeno-associated viral vectors, Ali *et al.* state that:

> "AAV vectors currently have a number of limitations: the virus is very difficult to prepare to high titres and without contamination with helper AV. The maximum size of insert that the vector is able to accommodate is only 4.7 kb. In addition, it now appears that transduction by AAV may require coinfection of cells with (contaminating) wild-type AV which may facilitate the conversion of ssDNA to the ds form. These problems will need to be addressed before AAV vectors can be considered suitable vectors for gene delivery in humans." (See p. 7, 2nd pragraph).

Additionally, Ali *et al.* conclude that improvements to the currently available vector systems are required, as well as increasing the efficiency of transduction of photoreceptor cells and increasing the duration of expression. Additionally, Ali *et al.* state that the problem of immune responses should also addressed before clinical trials can be contemplated (see *Conclusion*, page 11).

Note that the above cited art clearly indicates at the time of filing, the unpredictable status of the gene therapy art, in general sense, and in particular, as it specifically pertains to ocular gene therapy. Although specific vectors, promoters, genes and routes of administration might be or may have been effective for treatment of a specific disease providing a specific therapeutic effect, gene therapy, as a broad-based art, is clearly unpredictable in terms of achieving levels of duration and expression of a particular gene of interest (in this case Flt-1) which results in a therapeutic effect. As such, evidence pertaining to a specific vector, gene, promoter, route of administration, and therapeutic effect must be correlative to what is claimed. In the instant application, a correlation cannot be drawn for the reasons discussed in the preceding paragraphs. As established by the state of the art of gene therapy, note that therapeutic expression is not an inherent feature in methods of either *in vivo* or *ex vivo* gene transfer involving expression of a protein of interest. In fact, the lack of a therapeutic response in many gene therapy protocols attests to the unpredictable and undeveloped status of the art of gene therapy. The lack of correlative teachings in the art at the time of filing for gene therapy, as a

whole, makes it incumbent upon the specification to provide guidance that leads to a therapeutic outcome. In the instant specification, while the intraocular co-administration of rAAV-VEGF and rAAV-sFlt-1 inhibited the formation of neovascular disease, there is no correlation between the observed results and the inhibition of neovascular disease by the administration of a gene delivery vector that directs the expression of an anti-angiogenic factor. As discussed previously, the specification only provides support for the co-administration of the described vectors, and further, the specification fails to provide guidance or teachings with regard to which individuals would be at risk to development of neovascular diseases of the eye, such that one could inhibit the formation of the disease.

Note also, that the issue of "correlation" is dependent upon the state of the art at the time of the invention. MPEP § 2164 discusses that if one skilled in the art cannot readily anticipate the effect of a change within a subject matter to which the claimed invention broadly pertains, then there is a lack of predictability in the art. As the presently claimed subject matter pertains to ocular gene therapy, and with regard to the teachings of Romano *et al.* and Ali *et al.*, it is noted that there is significant art-recognized unpredictability in ocular gene therapy and the artisan cannot anticipate a therapeutic effect. Thus, what is known in the art provides evidence as to the question of predictability.

As such, in light of the state of the art of gene therapy, the specification fails to provide guidance for any of the above parameters for *in vivo* gene expression, nor

does the specification provide a clear correlation to carrying out gene therapy with regard to any particular effect by practicing the claimed method.

Accordingly, in view of the lack of guidance or teachings provided by the specification with regard to inhibition of neovascular disease by administration of soluble Flt-1, as well as the unpredictable and undeveloped state of the art with respect to the gene therapy art, as well as to the art of gene therapy of the eye, it would have required undue experimentation for one skilled in the art to make and/or use the claimed vectors and methods of using the same.

*Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 22 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Kendall *et al.* (**PNAS**, Vol. 90, November 1993, pp. 10705-10709).

Claim 22 is directed to a gene delivery vector which directs the expression of a neurotrophic factor, or an anti-angiogenic factor. Claim 26 is directed to the gene

delivery vector of claim 22, wherein said anti-angiogenic factor is soluble Flt-1, PEDF or soluble Tie-2 receptor.

Kendall *et al.* teach the cloning of soluble FLT into the plasmid pGEM3Z (see p. 10706, *Expression*).

Accordingly, Kendall *et al.* anticipate claims 22 and 26.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 22, 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kendall *et al.* (**PNAS**, November 1993, Vol. 90, pp. 10705-10709) when taken with Bujard *et al.* (US Pat No. 5,814,618, Sept. 29, 1998)

Claim 22 is directed to a gene delivery vector which directs the expression of a neurotophic factor, or an anti-angiogenic factor. Claim 27 is directed to the gene delivery vector of claim 22, wherein the vector is derived from a retrovirus. Claim 28 is directed to the gene delivery vector of claim 27, wherein the retrovirus is HIV or FIV. Claim 29 is directed to the gene delivery vector of claim 22, wherein the vector is generated from a recombinant adeno-associated virus.

Kendall *et al.* teach the isolation and cloning of the anti-angiogenic factor, soluble FLT (see p. 10705, 2nd column). Kendall *et al.* differ from the claimed invention in that they do not disclose cloning soluble FLT into a retroviral vector generated from either HIV or FIV. However, prior to the time of filing, Bujard *et al.* teach the construction of vectors that can be used to regulate gene expression. Bujard *et al.* teach that these vectors can be derived from a virus, such as replication defective retroviruses or adeno-associated viruses (see col. 12-13, bridging paragraph). Further, Bujard *et al.* teach that a gene that can be expressed using the described vector can be soluble receptors, such as soluble TNF receptor (see col. 37, lines 6-16).

Accordingly, in view of the teachings of Bujard *et al.*, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to use clone the soluble FLT described by Kendall *et al.* into the vectors described by Bujard *et al.* with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as the vectors described by Bujard *et al.* could more efficiently transfect cells *in vivo* to examine gene function.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear and convincing evidence to the contrary.

*Conclusion*

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thái-An N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to William Phillips, Patent Analyst, at (703) 305-3482. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

TNT
Thái-An N. Ton
Patent Examiner
Group 1632

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800